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FEATURED ORIGINAL RESEARCH ARTICLE

Sepsis Bundle Adherence and Early Vasopressor Administration in Pediatric Septic Shock: Secondary Analysis of Outcomes in a 2023 Multicenter Cohort in Bolivia

Raul Copana-Olmos, MD, MsC[1,2]
Nils Casson, MD[3]
Willmer Diaz-Villalobos, MD[4,5]
Victor Urquieta-Clavel, MD[6]
Mary Tejerina-Ortiz, MD[6]
Miguel Cespedes-Lesczinsky, MD[7]
Vladimir Aguilera-Avendaño, MD[6]
Maricruz Fernández-Vidal, MD[8]
Mariel Forest-Yepez, MD[4]
Danny Blanco-Espejo, MD[9]
Ibeth Rivera-Murguia, MD[10]
Claudia Castro-Auza, MD[9]
Milenka Gamboa-Lanza, MD[11]
Jhovana E. Paco-Barral, MD[12]
Gustavo Choque-Osco, MD[13]
Betzhi Vera-Dorado, MD[14]
Carol Mendoza-Montoya, MD[15]
Magbely Cuellar-Gutierrez, MD[7]
Jaime Fernandez-Sarmiento, MD, PhD[16,17]

OBJECTIVES: In a cohort of children with septic shock, we evaluated the association between vasoactive agent use within 1 hour of starting our sepsis bundle and mortality. Secondarily, we assessed the relationship between sepsis bundle adherence and mortality and other outcomes.

DESIGN: Nonpreplanned, secondary analysis of a national multicenter dataset collected in a resource-limited setting.

SETTING: Dataset from 14 centers in Bolivia collected between January 2023 and December 2023.

PATIENTS: Children under 15 years old with sepsis or septic shock defined using altitude-adjusted Phoenix criteria.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We included 268 patients in this secondary analysis, with median (interquartile range [IQR]) age 17 months (IQR, 6–63 mo). The sepsis bundle was used within 3 hours in 131 of 268 patients (49%). Vasopressors were used in 102 of 268 patients (38%) and 85 of 102 (83%) had received peripheral administration within the 1 hour of persistent hypotension, without any record of adverse events. Early vasopressor use within 1 hour of septic shock recognition, and antibiotic administration within 1 hour of sepsis recognition, were independently associated with lower odds (using adjusted odds ratio [aOR] and 95% CI) of mortality, respectively: 0.49 (95% CI, 0.28–0.89) and 0.41 (95% CI, 0.24–0.71; both $p = 0.001$). Failure to complete the sepsis bundle within 3 hours was associated with greater odds of mortality (aOR, 3.61 [95% CI, 1.64–7.91]; $p = 0.001$) and greater odds of longer interval before emergency consultation (aOR, 1.04 [95% CI, 1.01–1.07]; $p = 0.023$).

CONCLUSIONS: Early initiation of vasoactive agents in children with septic shock and timely sepsis bundle completion were independently associated with lower hazard of mortality. Historically, in Bolivia in 2023, bundle adherence was suboptimal, yet feasible interventions were associated with greater odds of better outcomes in pediatric sepsis and septic shock.

KEYWORDS: children; critical care; resource-limited settings; sepsis; septic shock; treatment

The 1990–2017 Global Burden of Disease identifies pediatric sepsis as a leading causes of child mortality, particularly in low- and middle-income countries (LMICs) (1); as shown by multicenter data from ten Latin American tertiary centers (2019–2021) (2). The 2020 Surviving Sepsis Campaign (SSC) and the 2022 Latin American Pediatric Intensive Care Society Task Force

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RESEARCH IN CONTEXT

- Previous evidence on early vasopressor use in children with septic shock is limited and largely based on small-scale pediatric data.
- There are no contemporary, multicenter studies describing the associated influence of pediatric sepsis bundle adherence and outcome in resource-limited settings.
- We have therefore carried out a secondary, nonpreplanned analysis of a 2023 dataset collected from 14 centers in Bolivia to identify associations between interventions and outcomes in pediatric sepsis and septic shock.

guidelines recommended early recognition and timely intervention to reduce sepsis-related mortality (3, 4). Emphasizing first-hour bundles including early sepsis recognition, oxygen administration in cases of pulse oximetry desaturation, resuscitation with crystalloid, broad-spectrum antibiotics, and early use of vasopressors. However, adherence to all bundle elements was only 13% in our prior Latin American study (2).

Since adherence to all components of a pediatric sepsis bundle may improve patient outcomes, we tested this hypothesis by carrying out a secondary, nonpreplanned analysis of a dataset collected in a LMIC from 14 centers in Bolivia (between January 2023 and December 2023) for the purpose of the 2024 Phoenix Criteria for sepsis and septic shock (5–7). Our primary objective was to evaluate the association between vasoactive agent use within 1 hour of starting our sepsis bundle and mortality in those with septic shock. Secondarily, we assessed the associations between sepsis bundle adherence and mortality and other outcomes.

METHODS

We analyzed data from 14 Bolivian hospitals—six pediatric referral and eight generals with pediatric emergency departments (EDs) and PICUs—collected between January 2023 and December 2023 for the LMIC Phoenix criteria study for sepsis and septic shock (5, 6). The Bolivian Sepsis Research Network used these data to describe national sepsis epidemiology and evaluate altitude adjustments to the Phoenix criteria (7). In June 2024, the Research and Bioethics Committee (Institutional Research Board [IRB]) at the Hospital del Niño Manuel Ascencio Villarroel approved this secondary, nonpreplanned analysis of the 2023 study (IRB 391459 approved with waiver of consent; study title "Multicenter retrospective evaluation of the Adherence to Pediatric Sepsis Bundles in a 2023 Cohort in a LMIC). In this current work, all research procedures were performed in accordance with the Helsinki Declaration of 1975.

In the current report, we focused on children under 15 years old with Phoenix-defined sepsis or septic shock (with the adjustments for altitude) presenting to the ED (5–7). We excluded patients with gestational age younger than than 37 weeks; neonatal hospitalization; inter-PICU transfers, patient with greater than 48 hours of preexisting sepsis treatment, and complex congenital heart disease; and those in palliative care. All participants centers used a standardized monitoring checklist, which included: documented availability of a PICU bed; dedicated pediatric ED and pediatric intensivists; and a 24-hour laboratory.

In this analysis, we used existing medical records, which were reviewed by the research team to ensure consistency in data collection and to define all relevant management variables for analysis. Missing data were treated as absent, as per our previous report using the 2023 dataset (7).

Time zero was defined as ED triage, direct PICU admissions, or specialist referral time (i.e., when PICU specialists were first involved) for inpatients. All triage criteria were determined using the Pediatric Assessment Triangle tool (8). Sepsis was clinically recognized by ED or PICU physicians. However, for study purposes, we retrospectively applied the Phoenix Sepsis Score (PSS) to confirm the diagnosis (5).

Bundled Care

Management bundles within the first 1 hour of care were based on the 2020 SSC guidelines (3). Oxygen therapy or endotracheal intubation in cases of respiratory failure. Antibiotics prescribed by the treating physician within the first 1 hour for septic shock and within the first 3 hours for sepsis. Fluid resuscitation delivered in aliquots of 10–20 mL/kg over 15–20 minutes in patients with clinical signs of low cardiac output (e.g., abnormal heart rate, hypotension, prolonged capillary refill, altered mental status, and decreased urine output), additional

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crystalloid boluses up to a maximum of 40–60 mL/kg within the first 1 hour or until signs of fluid overload were evident. Vasoactive agents' infusions after 20 mL/kg of fluid resuscitation if perfusion or blood pressure remained abnormal, or earlier if fluid overload was suspected or further fluid administration was contraindicated. Blood cultures obtained upon admission and before antibiotic administration. All decisions regarding the dosage and timing of bundle components were left to the attending physician discretion, although guided by the 2020 SSC recommendations (3).

Additional variables evaluated included 24-hour fluid balance after admission, capillary refill time in the upper extremity, and plasma biomarkers such as complete blood count, C-reactive protein, procalcitonin, electrolytes, arterial or venous partial pressure of blood gases, and other laboratory values obtained either as first measurements, or values at the time of ED admission.

Outcomes and Statistical Analysis

The primary outcome was mortality associated with the initiation of vasoactive agents within the first 1 hour of care in children with PSS defined septic shock. Secondary outcomes included relationships between bundle adherence components and mortality or clinical outcomes.

Descriptive data are presented as percentages and proportions, means, or medians. Hospital-free days were calculated as the total days alive and out of the hospital during the first 28 days following inclusion. We used Fisher exact, chi-square, or Wilcoxon rank-sum test. Multivariable logistic regression identified mortality associations, adjusting for age, symptoms duration, and illness severity according to the PSS, reporting adjusted odds ratios (aORs) with 95% CI. Kaplan-Meier curves and hazard ratios (HRs) were generated for survival analysis. Analyses was performed using the R statistical software version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In 2023, 2155 patients were screened across 14 PICUs; 268 met inclusion criteria (**Fig. S1** and **Table S1**, https://links.lww.com/PCC/C675). Overall, 183 of 268 patients (68%) were male and the median age was 17 months (interquartile range [IQR], 6–63 mo). Phoenix-defined septic shock occurred in 136 of 268 patients (51%) with a median Phoenix score of 4 points (IQR, 3–5 points); overall mortality was 89 of 268 (33%). Nonsurvivors had a longer duration of symptoms before first medical contact than survivors (4 vs. 3 d; $p = 0.023$).

Early Initiation of Vasoactive Agents and Mortality

Vasoactive support was required in 103 of 268 patients (38%; **Fig. 1**). Peripheral or central vascular access was obtained in 260 of 268 cases (97%), while intraosseous in eight of 268 (3%). Early vasoactive support (first 1-hr) occurred peripherally in 85 of 103 patients (82%) without adverse events recorded. Early vasoactive support was associated with lower odds of mortality (aOR, 0.49 [95% CI, 0.28–0.89]; $p = 0.020$), independent of age, illness severity, and symptom duration before presentation, compared with delayed initiation (**Table 1**). Vasoactive agents used were: norepinephrine alone in 50 (49%) cases; epinephrine alone in 30 (29%); a combination of norepinephrine and epinephrine in 11 (11%); and dopamine or dobutamine in the remaining 12 (11%) cases. The median duration of vasoactive support was 3 days (IQR, 2–6 d; **Table S2**, https://links.lww.com/PCC/C675).

Other Bundle Components and Outcomes

The first 1-hour crystalloid volume was similar between nonsurvivors vs. survivors (28 mL/kg [IQR, 20–60 mL/kg] vs. 30 mL/kg [IQR, 18–60 mL/kg]; $p = 0.612$). Fluid overload exceeding 10% of admission body weight at 24 hours occurred in 59 of 268 cases (22%), and we failed to identify an association between this endpoint and outcome. Regarding fluid responsiveness after the initial bolus, a lower proportion of nonsurvivors responded compared with survivors (30% [24/89] vs. 62% [101/179]; mean difference, 32%; 95% CI, 19.5–42.9%; $p < 0.001$; Table S2, https://links.lww.com/PCC/C675).

Supplemental oxygen was given to 233 of 268 patients (87%). We failed to identify an association between median Fio_2 and outcome (Table S1, https://links.lww.com/PCC/C675). A total of 90 of 268 patients (34%) required endotracheal intubation in the ED due to respiratory failure. Again, we failed to identify an association between proportion undergoing early intubation

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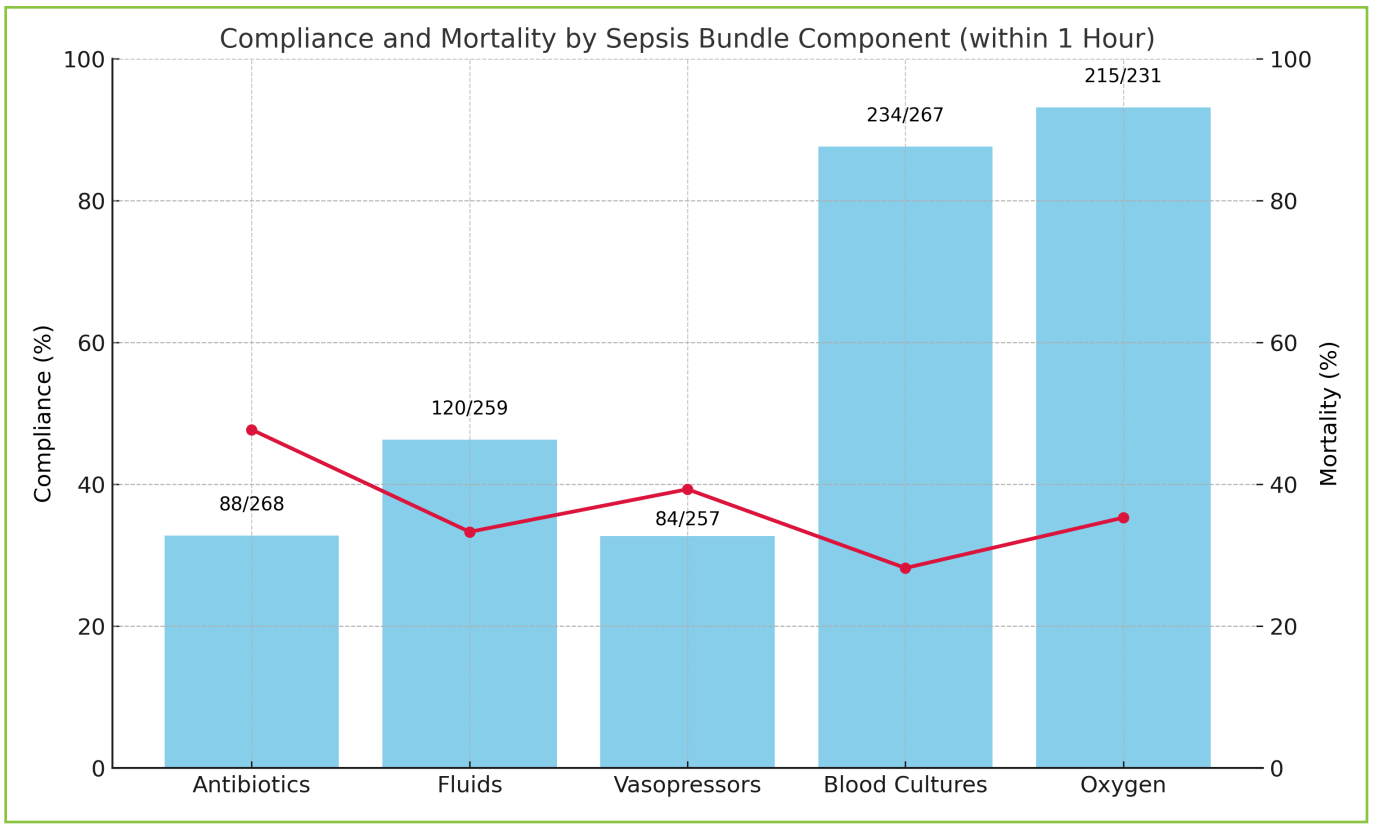

Figure 1. Compliance and associated mortality for pediatric sepsis bundle components administered within the first 1 hr. *Bar graph* showing the percentage of patients (with sepsis or septic shock) who received each core component of the sepsis bundle within the first hour after triage. Actual proportions (*n*/*N*) are presented above *each bar* to reflect the absolute number of patients who received each intervention. The *overlaid line* indicates the corresponding mortality rate among patients who received each intervention within the specified timeframe. The protocol applied either the 1- or 3-hr bundle based on illness severity. This *dual-axis* display aims to illustrate the inverse association between early bundle compliance and mortality.

TABLE 1.
Multivariable Logistic Regression Analysis of Mortality and Early Sepsis Bundle Compliance in Critically Ill Children

Variable	Adjusted OR (95% CI)	*p*
Duration of symptoms before initial clinical assessment	1.04 (1.01–1.07)	0.023
Antibiotics within first 3 hr in sepsis	0.32 (0.15–0.68)	0.003
Antibiotics within the first 1 hr in septic shock	0.41 (0.24–0.71)	0.001
Vasoactive support within first 1 hr	0.49 (0.28–0.89)	0.020
First 1 hr fluid volume	0.82 (0.41–1.59)	0.541
FIO_2	1.01 (0.99–1.03)	0.076
Noncompliance with the sepsis bundle within the first 1 hr	2.41 (1.29–4.50)	0.006
Noncompliance with the sepsis bundle within the first 3 hr	3.61 (1.64–7.91)	0.001

OR = odds ratio.
Results are based on a logistic regression model adjusting for age, duration of symptoms before initial medical evaluation, and illness severity according to the Phoenix Sepsis Score.

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and outcome (nonsurvivors vs. survivors: 33/89 [38%] vs. 57/179 [32%]; mean difference, 6% [95% CI, –5.8% to 18.2%; $p = 0.472$). During hospitalization, 209 of 268 patients (80%) were supported with mechanical ventilation. This support was associated with outcome, with use in a greater proportion of nonsurvivors compared with survivors (79/89 [91%] vs. 130/179 [75%]; mean difference, 16% [95% CI, 6.3–24.1%]; $p = 0.005$). Other details are summarized in Table S2 (https://links.lww.com/PCC/C675).

Antibiotics were administered in 259 of 268 cases (97%). Survivors received them earlier (median 60 min [IQR, 30–60 min]) than nonsurvivors (64 min [IQR, 40–180 min]; $p = 0.002$). Of note, in survivors the upper quartile was 60 minutes, meaning that close to 25% of cases received antibiotics after the 60-minute mark. In contrast, nonsurvivors showed a wider distribution, reflecting that 25% of these cases received antibiotics after 180 minutes. In septic shock, survival was higher when antibiotics were started within the first 1 hour (133/179 [74%] vs. 47/89 [53%]; mean difference, 21% [95% CI, 8.8–32.8%]; $p < 0.001$). In children with sepsis survival was higher when receiving antibiotics within the first 3 hours (163/179 [93%] vs. 67/89 [79%]; mean difference, 14% [95% CI, 5.4–24.0%]; $p = 0.003$; Table S2, https://links.lww.com/PCC/C675).

Blood cultures were obtained in 233 of 268 cases (87%). On comparing pathogen isolation in nonsurvivors vs. survivors, we failed to identify an association (29/66 [44%] vs. 58/168 [35%]; mean differences, 9% [95% CI, –4.6% to 22.8%]; $p = 0.131$). The most frequently isolated pathogen was *Staphylococcus aureus* (21/233 [9%]), followed by *Klebsiella pneumoniae* (10/233 [4.3%]), *Escherichia coli* (9/233 [3.9%]), and *Streptococcus pneumoniae* (4/233 [1.7%]) of cases. The most common infectious source was respiratory (129/268 [48.1%]), followed by gastrointestinal (98/268 [36.6%]) and other foci (41/268 [15.3%]).

Bundle Compliance

Sepsis bundle adherence was achieved in 112 of 268 patients (42%) within the first 1 hour and in 131 of 268 patients (49%) within the first 3 hours (**Table S3**, https://links.lww.com/PCC/C675). Bundle completion within the first 3 hours was associated with lower hazard of death (HR, 0.31 [95% CI, 0.14–0.75]; $p = 0.008$; **Fig. 2**). Among nonsurvivors, the median survival time in the PICU was 3 days (IQR, 1–7 d), and the total median survival time was 4 days (IQR, 1–11 d), consistent with early mortality due to sepsis. In contrast, survivors had a median PICU stay of 7 days (IQR, 4–12 d), and a hospital-free days count of 12 days (IQR, 5–18 d; Table S3, https://links.lww.com/PCC/C675).

DISCUSSION

In this secondary, nonprespecified analysis of a 2023 dataset of pediatric sepsis/septic shock from 14 Bolivian centers, we made three key observations about sepsis bundle adherence. First, in our LMIC setting, patients presenting to the ED or already hospitalized in the PICU showed low adherence to complete sepsis bundle care. Second, initiation of vasopressors within the first 1 hour of care—via peripheral or central venous access—was associated with lower odds of mortality. And, third, early administration of antibiotics within the first 1 hour for septic shock, and within the first 3 hours of sepsis, was associated with survival. Taken together, failure to adhere to the sepsis bundle was associated with greater odds for mortality.

Sepsis bundle adherence was achieved in 42% of patients within the first 1-hour and 49% of patients within the first 3 hours of care. This 2023 compliance rate appears to be an improvement on the 13% found in the 219 pediatric sepsis patients managed in ten tertiary centers in Latin America, 2019–2021—including

AT THE BEDSIDE

- In children managed in 14 centers in Bolivia in 2023, we have found that out of 102 patients receiving vasopressors as part of the sepsis bundle, 83% had received peripheral venous administration without any record of adverse events.
- Of note, administration of vasopressors within 1 hour of recognizing septic shock was associated with lower odds of mortality.
- Secondarily, even though adherence to the full sepsis bundle in 2023 was low, administration of antibiotics within 1 hour of septic shock recognition was also associated with greater odds better clinical outcomes.

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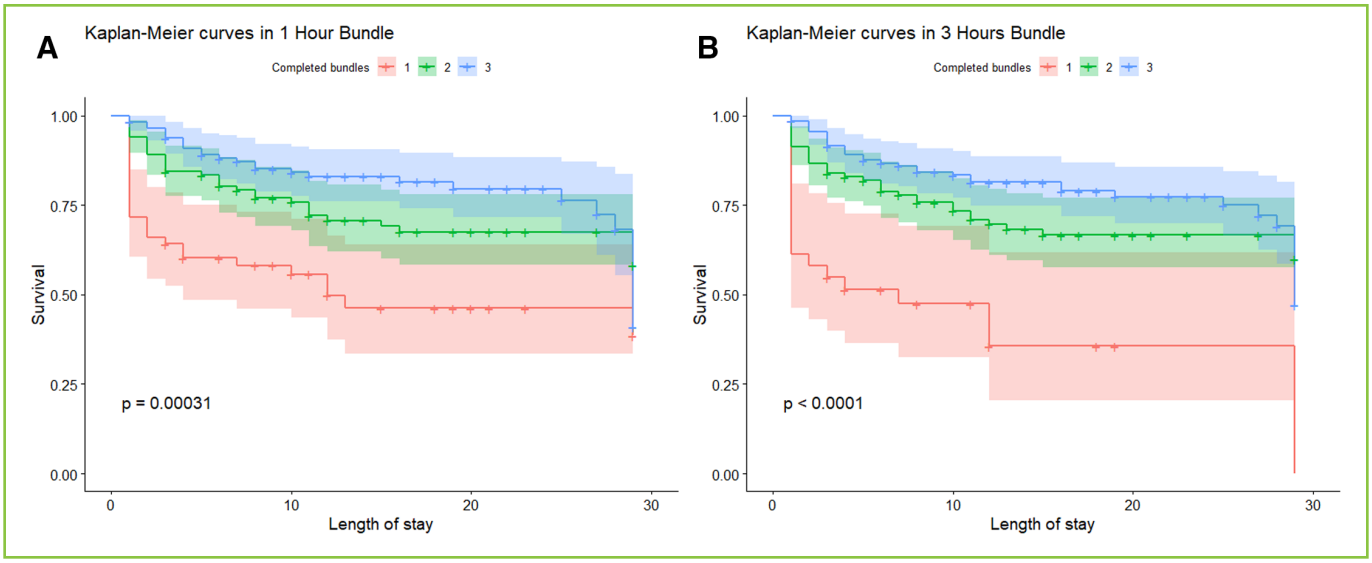

Figure 2. Kaplan-Meier survival curves according to 1- and 3-hr sepsis bundle compliance. **A**, Survival probability stratified by the number of bundle components completed within the first 1 hr. Receipt of all three bundle components was associated with higher survival rate compared with those receiving only one or two components. **B**, Comparison of survival according to the timing of full bundle completion (within 1 hr vs. after 1 hr). Early bundle adherence was associated with improved survival.

one Bolivian site (2). Nevertheless, there is clearly room for improvement, particularly when one considers that in 2023 physicians at all 14 centers followed 2020 SSC recommendations (3). Beyond sepsis recognition and new 2024 PSS criteria (9–11), studies should be focused on practice implementation. For example, a Thai single-center, pre- vs. post-implementation study of an institutional guideline for pediatric septic shock care (2014–2016 vs. 2017–2022) showed increased use of peripheral inotropes and noninvasive cardiac monitoring, with a number needed to treat of 6 patients to prevent one death (12). Conversely, a French multicenter study in 21 pediatric EDs (2021–2022) highlighted persistent gaps in applying SSC-based protocols (13).

Regarding early vasopressors use, we found that compared with nonsurvivors, a greater proportion of survivors received vasopressors within 60 minutes of care, and was associated with reduced mortality, regardless of patient age or duration of symptoms before presentation. On closer inspection, of the 103 patients receiving vasopressor support, 60% received norepinephrine (49% alone, 11% in combination with epinephrine). A systematic review of 12 studies up to 2024, in 748 fluid-refractory septic shock patients, reported a pooled mortality of 12% (95% CI, 6–21%). In the review, norepinephrine use was associated with the lowest mortality rate, although the majority of data came from nonrandomized studies. Interestingly the use of two vasoactive agents resulted in lower mortality than the use of a single agent (14). These observations are especially relevant in LMIC settings, where delays in advanced hemodynamic monitoring or central venous access placement may hinder timely interventions (15). Which leaves us with two important questions to consider.

First, how should we now approach fluid resuscitation during the escalation in interventions for pediatric sepsis? Physiologically, early vasopressor initiation may mitigate the consequences of prolonged hypotension, limit capillary leak and interstitial edema, and support coronary and cerebral perfusion at a time when myocardial dysfunction and vasoplegia frequently coexist in pediatric septic shock (16). The intravascular effect of fluid boluses is often short-lived, and up to 50% of patients show poor fluid responsiveness due to underlying myocardial depression or vasodilation (17). Our findings support not delaying vasopressors in children who fail to respond promptly to initial fluid resuscitation (18–20). And, to this end, it was encouraging to note that in our 2023 cohort in a LMIC setting, 82% of vasoactive infusions were administered via peripheral venous access without record of adverse events. Notwithstanding this observation, poor fluid responsiveness in our cohort was associated with greater odds of mortality, likely reflecting more severe shock, underlying circulatory failure, or comorbid conditions

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that limited the effectiveness of fluid resuscitation. Such patients often require earlier vasopressor support, suggesting that timely recognition of this clinical profile may help prevent fluid overload and support a more effective, individualized resuscitation strategy. The ongoing "Septic shock reversal is quicker in pediatric patients randomized to an early goal-directed fluid-sparing strategy vs. usual care (SQUEEZE) trial" exhibited earlier septic shock reversal (21). Interestingly, in this trial, the fluid-sparing resuscitation strategy involved avoidance of fluid bolus therapy beyond 40 mL/kg and immediate initiation and preferential escalation of vasoactive medication support—which was similar to the median fluid volume used in our Bolivian cohort.

Second, early vasopressor use makes Phoenix criteria for septic shock somewhat circular, as vasopressor initiation itself defines shock (9, 22, 23). Then, a corollary question is having initiated vasopressor therapy, what is the blood pressure target to be used in sepsis or septic shock patients? Is it greater than the age-specific 5th percentile as used in the yet to be published SQUEEZE trial (21), or the ongoing Permissive Blood Pressure Target versus Usual Care in Critically Ill Children with hypotension (PRESSURE) randomized controlled trial involving 1500 patients (24)? Or, as suggested in a single-center, open-label, randomized noninferiority trial carried out in 144 pediatric septic shock cases in India (2021–2024), there is no difference in targeting the 5th or 50th percentile in mean blood pressure and 28-day mortality (25, 26). We await the results of the SQUEEZE and PRESSURE studies and the respective implications for contemporary critical care.

Our third key observation was about timely antibiotic administration and its association with survival. This aligns with international pediatric sepsis guidance and meta-analyses showing increased mortality with each hour of delay in antibiotic administration (3, 4). Despite high overall antibiotic use in our 2023 cohort (97%), there was variability in the timing of treatment and this observation underscores the need to improve early recognition and rapid escalation in emergency care workflow. The target should be 100% timely administration in pediatric practice (27), even setting aside whether or not the appropriate antibiotic dosing has been carried out for sepsis-related altered pharmacokinetics and augmented renal clearance (28–30). In the context of all bundle components needing completion within the first 1 hour, and our definition of completeness (i.e., at least four of five bundle components) we found that compliance within 3 hours was associated with close to a 70% reduction in hazard of mortality. However, we acknowledge that our retrospective analysis does not permit causal inference due the potential for residual confounding despite multivariable adjustment. Taking all the above together, despite the logistical challenges, adherence to early sepsis bundles was feasible in our 14 centers, LMIC setting in Bolivia in 2023, reinforcing the relevance of these interventions (7). We believe that our data highlight the necessity for an ongoing structured response to clinical practice and training to improve timeliness and completeness of care.

In this nonpreplanned secondary analysis of pediatric sepsis data from 14 centers in Bolivia in 2023, there are five main limitations. First, our study had a retrospective design, which inherently limits the ability to establish causal relationships. Although we adjusted the models for age, symptom duration, and illness severity using the PSS, we acknowledge that advanced causal inference methods such as inverse probability of treatment weighting were not applied, which could have strengthened the robustness of our findings. Also, there were 89 deaths in our population, and we evaluated eight explanatory variables in the multivariable analysis, so there is some risk of statistical overfitting with less than 15 outcome events per variable tested. Second, variability in documentation across centers may have influenced time-to-intervention measurements. Third, although 14 hospitals were included, the total sample size remains modest, potentially limiting the power to detect smaller effect sizes. Fourth, selection bias may have occurred, as the study only included patients who presented to EDs and had complete medical records. Last, certain clinical data—such as lactate measurements, echocardiography-based assessments of perfusion, or long-term outcomes—were not uniformly available and thus not included in the analysis.

In conclusion, in this 2023 multicenter cohort from Bolivia, conducted in a resource-limited setting among children with sepsis and septic shock, we observed low adherence to the treatment bundle. However, early initiation of vasopressors and timely administration of antibiotics were associated with reduced mortality. In contrast, delayed medical consultation and failure to

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complete the sepsis bundle within the first 1 hour and 3 hours were independently associated with higher mortality and worse clinical outcomes. These findings underscore the need for randomized clinical trials to evaluate the impact of early vasopressor initiation in pediatric septic shock.

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1 *Department of Pediatric Critical Care, Hospital del Niño Manuel Ascencio Villarroel, Cochabamba, Bolivia.*

2 *Department of IIBISMED, Faculty of Medicine, Universidad Mayor de San Simón, Cochabamba, Bolivia.*

3 *Division of Pediatric Intensive Care Unit, Hospital San Juan de Dios, Tarija, Bolivia.*

4 *Division of Pediatric Intensive Care Unit, HODE Maternoinfantil, Caja Nacional de Salud, La Paz, Bolivia.*

5 *Department of Pediatrics, Facultad de Medicina, Universidad Pública del Alto, El Alto, Bolivia.*

6 *Department of Pediatric Intensive Care Unit, Hospital del Niño Ovidio Aliaga Uria, La Paz, Bolivia.*

7 *Division of Pediatric Intensive Care Unit, Hospital Materno Infantil Boliviano Japones, Beni, Bolivia.*

8 *Pediatric Emergency Department, Hospital Obrero N°2, Caja Nacional de Salud, Cochabamba, Bolivia.*

9 *Division of Pediatric Intensive Care Unit, Hospital del Norte, La Paz, Bolivia.*

10 *Division of Pediatric Intensive Care Unit, Hospital de Niños Mario Ortiz Suarez, Santa Cruz, Bolivia.*

11 *Division of Pediatric Intensive Care Unit, Hospital Daniel Bracamonte, Potosi, Bolivia.*

12 *Division of Pediatric Intensive Care Unit, Hospital del Niño Sor Teresa Huarte Tama, Sucre, Bolivia.*

13 *Division of Pediatric Intensive Care Unit, Hospital de Trauma Corazon de Jesus, El Alto, Bolivia.*

14 *Division of Pediatric Intensive Care Unit, Hospital Caja Nacional de Salud, Oruro, Bolivia.*

15 *Department of Intensive Care, Hospital General San Juan de Dios, Oruro, Bolivia.*

16 *Department of Pediatrics and Intensive Care, Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, Colombia.*

17 *Department of Pediatrics and Intensive Care, Universidad de La Sabana, Chía, Colombia.*

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For information regarding this article, E-mail: r.copana@umss.edu.bo

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